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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/058,292	01/30/2002	James L. Hartley	0942.285000H/RWE/BJD	3058

26111 7590 03/23/2004

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,292	HARTLEY ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 35-225 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 35-225 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/11/03; 8/19/03; 11/4/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/2003 has been entered.

Receipt is acknowledged of a supplemental amendment, filed 1/5/2004 in response to a Notice of Nonresponsive amendment, in which several claims were amended (claims 36-39, 42, 69, 90, 93, 105, 116-117, 152-153, 158-162, 188-189, 211, 214-215, 219). Claims 35-225 are pending and under consideration in the instant application.

Any rejection of record not addressed in the instant office action is hereby withdrawn. This action is not final.

Information Disclosure Statement

Receipt is acknowledged of information disclosure statements (IDS's) filed on 8/11/2003, 8/19/2003 and 11/4/2003. A signed and initialed PTO Form 1449 corresponding to each IDS has been mailed along with this action. Pending applications listed on the PTO Form 1449's have been considered, but have been crossed out since these applications are not considered references for publication on the face of any patent to issue from the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35-71, 74-77, 115-142, 145-180, 183-204, 207-220 & 223 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al (WO 93/19172, of record; see the entire application). **This is a new rejection.**

Johnson et al teach methods for producing members of specific binding pairs featuring the use of recombinant bacteriophage to display functional antibodies (e.g. scFv; see, for example, pages 19, 26-34, 46-47, 49 and 52). Their methods include a method of producing a nucleic acid molecule by providing a first nucleic acid molecule comprising a first portion of a gene and a recombination site, a second nucleic acid molecule comprising a second protein of a gene and a recombination site, mixing *in vitro* or *in vivo* the first and second nucleic acids with a recombination protein to recombine the first and second nucleic acids to form a third nucleic acid, thereby forming an operably linked and functional gene from the first and second portions of the gene. Johnson et al teach the recombination of immunoglobulin genes in a phage that expressed the recombined immunoglobulin genes by joining the recombined immunoglobulin with a promoter that causes the expression of the recombined immunoglobulin genes on the

surface of the phage (e.g. pages 26-34). The gene may encode a selectable marker or a heterodimeric product (e.g. pages 32 and 47). The first or second portion of the gene may be fragments of the gene and may comprise a promoter and may further be a PCR product (e.g. pages 32 and 52). The first and second portions of the gene may be located adjacent to the recombination site, and the first or second nucleic acid molecule may comprise a cloning site (e.g. pages 19, 26-27, 31-32 and 46). The first, second or third nucleic acid may be an expression vector and may be linear. The functional gene may be expressed in a host cell and may be selected (e.g. phage display). The host cell may be *E. coli* (e.g. pages 26-34). The recombination sites may be loxP sites or att sites. The recombination protein may be Cre, Int, IHF, Xis, Flp, gamma-delta, Tn3, Hin, Gin or Cin (e.g. pages 26-34). Johnson et al teach that additional recombination sites may be present on the recombination substrates (e.g. pages 22-23). Johnson et al teach that the vector FdDOG-1 is derived from pUC19, which has multiple cloning sites.

Response to Arguments

Applicant's arguments filed 8/11/2003 and 1/5/2004 in response to similar grounds of rejection have been fully considered but they are not persuasive. The previous grounds of rejection were primarily directed to *in vitro* embodiments. Applicants' response essentially argues that the Johnson et al application only mentions *in vitro* embodiments in passing and does not teach any of the specifics required for those embodiments such as relative DNA concentrations and/or concentration of recombination protein, etc. that would be required to practice the claimed *in vitro* methods. Essentially, the response argues that the Johnson et al reference is not enabling. Applicants arguments are not persuasive in that the alleged difficulties of performing *in vitro*

recombination between nucleic acids utilizing a site-specific recombinase such as Cre are unsupported by the instant application and the prior art. It would have only required routine experimentation to determine the optimal reaction conditions in order to practice the methods of Johnson *in vitro* with regard to utilizing a recombinase and its cognate recombination sites (e.g. Cre/LoxP or Int/att) to generate the nucleic acids of Johnson et al. Therefore, Johnson et al is considered enabling for the *in vitro* embodiments of the rejected claims.

It is noted that many of the rejected claims are directed to embodiments where either the first or second nucleic acid molecule comprise a "portion" of an antibiotic resistance gene and that the third nucleic acid molecule formed by recombination of the first and second nucleic acids comprises a promoter operatively linked to only a "portion" of the antibiotic resistance gene. The term "portion" is not explicitly defined in the specification and can be interpreted broadly to encompass even the smallest part of the antibiotic gene (e.g. a single nucleotide present in the given antibiotic gene). It is further noted that claim 78 and dependent claims were not rejected over Johnson et al on these grounds due to the limitation "...to form a functional antibiotic resistance gene...".

Claims 35-42, 49, 57-59, 66-71, 74-81, 88, 96-98, 102-106, 109-117, 124, 132-134, 138-142, 145-150, 159-163, 176-180, 183-189, 196-197, 201-204 & 207-212 are rejected under 35 U.S.C. 102(e) as being anticipated by Demirjian et al (U.S. Patent No. 5,981,177; see the entire patent). **This is a new rejection.**

Demirjian et al (i.e. the '177 patent) teach methods for generating random transcriptional or translational fusions comprising the use of modified transposons (e.g.

Mu transposon; the Abstract). In these methods a first nucleic acid molecule comprising a first portion of a gene and a recombination site, a second nucleic acid molecule comprising a second portion of a gene and a recombination site are mixed *in vitro* or *in vivo* with a recombination protein to recombine the first and second nucleic acids to form a third nucleic acid comprising an operably linked, functional gene (e.g. column 8, lines 9-11; columns 9-10; Figure 12, etc.). The gene may encode a selectable antibiotic marker or a structural gene. The first or second portion of the gene may be fragments of the gene and may comprise a promoter and may be PCR products (e.g. column 9, lines 39-60; column 16, lines 51-68). The first, second or third nucleic acid may be an expression vector, and may further be linear. The functional gene may be expressed in a host cell and may be selected based upon its expression. The host cell may be *E. coli*.

Response to Arguments

Applicant's arguments filed 8/11/03 and 1/5/04 have been fully considered but they are not persuasive. The responses essentially argue that the '177 patent does not teach each and every one of the claim limitations in that it does not teach the use of a mixture comprising a recombination protein. In support of this assertion, applicants cite passages from the specification that indicate that the Mu transposon has the ability to undergo high frequency random integration into nucleic acids in the absence of a recombination protein and that Demirjian et al teach the use of a temperature sensitive repressor in order to prevent unwanted transposition (see column 2, lines 57-65 and Example 6).

This argument is not persuasive due to the fact that *nowhere* in the '177 patent do the inventors teach that the invention is necessarily practiced without a transposase or

other recombination protein to mediate recombination. For example, the passage from column 2 of the specification merely indicates that a temperature sensitive repressor of transposition has been developed in the art to regulate the circumstances in which transposition occurs. It is further noted that in Examples 1-5, the inventors describe experiments *in vivo* where transposition was induced. Such transposition was necessarily mediated by some sort of recombination protein, whether or not it was a transposase, and necessarily satisfies the claim limitations regarding the presence of the recombination protein. Applicants' are directed to their own definition for what constitutes a "recombination protein" at page 14, lines 21-23: "Recombination proteins[:] include excisive or integrative proteins, enzymes, co-factors or associated proteins that are involved in recombination reactions involving one or more recombination sites. See, Landy (1994), *infra*." Under this definition, any protein that assists in mediating integration of the Mu elements taught by the '177 patent necessarily are recombination proteins. Example 6 is directed to only a subset of the transposable elements of the invention and is clearly not intended to be limiting by the inventors for all of the encompassed embodiments of their invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-225 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Each of the rejected claims recites the limitation "portions thereof" with reference to a first or second gene that are recombined to form a gene or "portions thereof". It is unclear the minimal part of a gene that can be considered as satisfying this limitation. For example, could a single nucleotide present in a first or second gene be considered as a "portion" of the gene in the context of the claims? Or is there some minimal functional requirement that is necessary in order to satisfy the claim limitation of being a "portion" of a first, second or product gene in the rejected claims?

Several of the claims recite the limitation that the first or second gene, or portion thereof, is located "adjacent" to a given recombination site (e.g. claims 57-58, 96-97, 132-133, 196-197). The term "adjacent" is not defined in the specification and it is unclear the structural/functional requirements for satisfying this limitation. Does the term necessarily mean that the recombination site is immediately adjacent to the gene or portion thereof, with no intervening nucleotides? Or can some unspecified number of nucleotides be present between the portion of the gene and the recombination site?

Some of the claims comprise the limitation of a nucleic acid molecule further comprising "at least one cloning site" (e.g. claims 98, 134. The term is not explicitly defined in the specification. Upon reading the specification, it appears the claims may be directed to a restriction site that can be used for insertion of desired heterologous sequences. Given that insertion of a desired, heterologous sequence can be accomplished at any site within a given DNA molecule using a variety of different techniques that don't require a restriction endonuclease, it is unclear what structural/functional characteristics are intended by the recited limitation of a "cloning site". It would be remedial to amend these claims to clearly indicate what is intended by the term "cloning site".

Claim 149 is vague and indefinite in that there is no clear and positive antecedent basis for the term "said nucleic acid" in claim 115, upon which claim 149 is dependent.

Claim 158 is vague and indefinite in that the metes and bounds of the phrase "...wherein said first gene or portion thereof, and said second gene or portion thereof, are the same" are unclear. It is unclear the degree to which the first and second genes are intended to be the same in the context of the invention. Performing the recombination reaction makes little sense if the entire gene (e.g. promoter, nontranslated sequences and coding sequences) is entirely the same, as is implied by the current language. It appears the limitation may be intended to specify that the portions of the first and second gene, or are obtained from the same gene and are recombined to reconstitute the original gene.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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